

Effect of Growth Hormone Deficiency on the Cardiovascular System

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Abstract: Growth hormone (GH) is a hormone responsible for the regulation of somatic cell growth, including the development of the heart and blood vessels, and their functions. GH deficiency is a clinical condition characterized by impaired activity, decreased quality of life, as well as the impaired composition of substances in the body. GH improves cardiac metabolism, reduces oxygen consumption and energy requirements, even in patients with heart failure who have increased wall stress and impaired glucose metabolism that is characterized by insulin resistance and fasting hyperinsulinemia. Patients with GH deficiency also suffer from abnormalities in coagulation factors, such as increased levels. In another study, young adult patients with GH deficiency were found to experience a decrease in left ventricular mass, decreased ejection fraction, as well as abnormal diastolic filling patterns. GH therapy significantly reduces low-density lipoprotein (LDL) cholesterol but does not affect triglyceride (TG). Growth hormone deficiency can increase the risk of cardiovascular disease by affecting the prevalence of risk factor-related events, such as central obesity, fat, and carbohydrate metabolism disorders, increased proinflammatory cytokines, endothelial dysfunction and oxidative stress, and morphological and cardiac dysfunction.

1 INTRODUCTION

Growth hormone (GH) is a hormone responsible for the regulatory process of somatic cell growth, including the process of development of the heart and blood vessels, and their functions. The effects of growth hormone possibility occur directly or indirectly, by stimulating the production of insulin-like growth factor-1 (IGF-1), which in turn bridges the growth hormone work against the peripheral tissue. Axis GH / IGF-1 primarily plays a role in the growth of heart cells, blood vessels, and myocardial tissue (Di Somma et al., 2017).

GH deficiency is a clinical condition characterized by impaired activity, decreased quality of life, as well as the impaired composition of substances in the body. The prevalence of GH deficiency in the population is about 1: 10,000 to 4: 10,000 (Monson et al., 2000). In recent years, there has been considerable discussion of cardiovascular risk in patients with growth hormone deficiency in adulthood (Giovannini et al., 2015).

GH deficiency negatively affects the cardiovascular system directly in the heart and blood vessels and indirectly by causing insulin resistance, abdominal obesity, hypercoagulability, elevated

serum lipids, and decreased exercise performance and pulmonary capacity (Castellano et al., 2009).

2 GROWTH HORMONE

GH peptides comprise 191 single-chain amino acids, synthesized and secreted by somatotrophic cells in the anterior pituitary gland. This hormone is tightly regulated by two hypothalamic neurohormones: GH releasing factor (GHRF) and Somatostatin (GH inhibitor).

In addition, GH modulates its own secretion in two ways, first indirectly by stimulating the production of insulin-like growth factor-1 (IGF-1), which inhibits somatotrophic cells and stimulates the secretion of somatostatin, and secondly, directly by inhibiting mRNA from GHRF and stimulating synthesis of somatostatin mRNA (Gunawardane et al., 2015). The secretion of growth hormone is episodic. GH secretion is enhanced by α 2-adrenergic agonists, hypoglycemia and day-to-day pressure. Its secretion is inhibited β dan α 1-adrenergic agonists, glucocorticoids, and aging (Castellano et al., 2009).

GH possibility causes its effects directly and indirectly. Most of the effects are indirectly mediated by induction of IGF-1 expression in the liver and peripheral tissue (Martinelli et al., 2008). IGF-1, a single-chain protein composed of 70 amino acids, has a homologous structure with insulin, synthesized in the liver and kidneys. IGF-1 circulates in a state bound to a protein carrier (IGFBPs). Serum concentrations of IGFBPs are influenced by GH levels in the circulation but do not possess a circadian rhythm. The intracellular signaling pathway involves transduction of IGF-1 via insulin receptor substrate (IRS) -1, (phosphatidylinositol) PI 3-kinase, phospholipase C (PLC) - β 1, mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase cascade (Castellano et al., 2009).

Decreased plasma concentrations of IGF-1 are caused by the decreased amplitude of age-related GH-related pulsations and increased resistance to GH effects. The mechanisms underlying this include peripheral influences (steroid gonads, adipose tissue), changes in neuropeptides and hypothalamic neurotransmitters, as well as increased secretion of somatostatin (Giordano et al., 2008.).

Although a decrease in GH/IGF-1 axis is associated with an increase in GH/IGF-1 receptors in cardiac myocytes, this increase fails to compensate for a decrease in GH secretion possibly due to reduced intracellular signal transduction (Follin et al., 2010).

GH/IGF-1 deficiency plays a role in the process of alteration of the cardiovascular system, such as reduced number of cardiomyocytes, decreased density of coronary arterioles, increased fibrosis and collagen deposition (Arcopinto et al., 2015), decreased protein synthesis and contractile protein changes and decreased myosin-actin bonding (Colao and Di Somma, 2002. , Isgaard, 2015).

3 PHYSIOLOGICAL GROWTH HORMONES

GH/IGF-1 axis plays a role in regulating the growth of heart cells, stimulating myocardial contractility, and affects the blood vessel system. Myocardium and endothelium not only express receptors for GH and IGF-1 but also produce IGF-1 locally. Therefore, there is a direct action of GH through the endocrine mechanism and indirect action via the autocrine/paracrine mechanism of IGF-1 (Di Somma et al., 2017).

In the blood vessels, the GH/IGF-1 axis has an effect by activating the nitric oxide (NO) system and regulating it independently of the NO endothelial receptors. NO production causes relaxation of the smooth muscle of the arteries, thereby decreasing vascular tone. In addition, NO inhibits the proliferation and migration of smooth cellular muscle, decreases platelet adhesion, and reduces lipooxygenase activity and the formation of oxidized LDL-c (Di Somma et al., 2017).

Recently, NO has been shown to modulate the function of the cardiac cytoskeleton by altering the sensitivity of the myofilaments to calcium. In addition, IGF-1 possibility causes vasorelaxation in two ways, first by increasing Na/K-ATPase activity and secondly by regulating gene expression of the potassium channel, which play an important role in regulating the tone of blood vessels in the smooth muscle of blood vessels (Setola et al., 2008).

The GH/IGF-1 axis also regulates the growth and metabolism of heart cells, by increasing the uptake of amino acids, protein synthesis, cardiomyocyte size and expression of certain myocyte genes. IGF-1 specifically stimulates heart muscle cell hypertrophy and increases the transcription of certain elemental protein genes, such as Troponin I, myosin light chain-2, and α -actin (Di Somma et al., 2017).

In addition, IGF-1 triggers the synthesis of collagen by fibroblasts, in which GH increases the rate of collagen deposits in the heart. Several studies have shown that IGF-1 affects the growth of heart cells by reducing the apoptosis of myocytes of the heart (Isgaard, 2015).

In addition to the above, the GH/IGF-1 axis also controls the contractility of the heart through several mechanisms, among others, by increasing the sensitivity of calcium myofilaments, modifying intracellular calcium levels through increased Ca²⁺ L-type channel activity and up-regulation of the amount of Sarcoplasmic reticulum ATPase (SERCA). Up-regulation of SERCA will lead to increased contractility, increase the amount of calcium stored in the sarcoplasmic reticulum, and make the calcium peak level higher when there is a stimulus (Lombardi et al., 2012).

Growth hormone also induces the conversion of myosin into a V3 isoform whose activity requires only low ATPase. The prevalence of isoform V3 increases the number and duration of crosslinking of myosin-actin, and increases the sensitivity and availability of calcium causing the myocardium to function and be more energy efficient. Isoform V3 also remains in large quantities in hypertrophy caused by excess fluid volume, to compensate for

the decrease in contractility and high wall stress (Arcopinto et al., 2015).

Growth hormone causes the conversion of metabolic energy into a process of contraction and increases the intrinsic ability of the myofilaments to increase their contraction force, resulting in improved left ventricular performance. In conclusion, GH improves cardiac metabolism, reduces oxygen consumption and energy requirements, even in patients with heart failure who have increased wall stress (Follin et al., 2010).

4 PATHOPHYSIOLOGICAL GROWTH HORMONES

The prevalence of GH deficiency in the population is about 1: 10,000 to 4: 10,000 (Monson et al., 2000). Recently, there has been considerable discussion of cardiovascular risk in patients with growth hormone deficiency in adulthood. GH deficiency negatively affects the cardiovascular system directly in the heart and blood vessels, indirectly by causing insulin resistance, abdominal obesity, hypercoagulability, elevated serum lipids, and decreased exercise performance and pulmonary capacity (Giovannini et al., 2015).

4.1 Atherosclerosis and Ischemic Heart Disease

GH deficiency is associated with increased atheroma plaque in the carotid artery and femoral artery when compared with healthy controls. Other atherosclerotic markers of GH deficiency are indicated by an increase in the thickness of the intima tunica and the media tunica in the common carotid artery and aortic aorta (Castellano et al., 2009). Increased intima-media thickness (IMT) is one of the signs of premature atherosclerosis that is directly related to death caused by Acute coronary syndrome (Di Somma et al., 2017).

One of the most commonly used parameters for IMT assessment is IMT in the common carotid artery. Some studies show lower CIMT values in groups with higher IGF levels. One study showed an increase in mean BMI in patients with GH deficiency with low IGF-1 levels, with $p < 0.001$, showing significant differences between the two groups (Di Somma et al., 2017). The study also suggested that serum IGF-1 levels were strongly associated negatively with IMT values in the common carotid artery ($r = -0.84$, $p < 0.00001$).

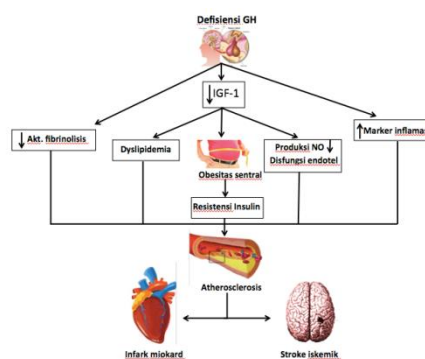


Figure 1: Effect of growth hormone deficiency on the cardiovascular system (Di Somma et al., 2017; Gunawardane et al., 2015).

The process of atherosclerosis is slowed by high levels of IGF-1 levels visible in patients with high IGF-1 levels had lower CIMT values. In recent years, many studies have investigated the association between low levels of IGF-1 and the risk of ischemic heart disease and stroke where patients with lower serum IGF-1 levels will have an increased risk of coronary heart disease as much as 1.27 to 1.94 times greater than controls (Laughlin, 2004).

Studies in Japanese populations show an increased risk of myocardial infarction in hypopituitarism patients not receiving GH therapy (Mo et al., 2014). The same study also showed a higher incidence of angina pectoris risk in patients with GH deficiency (2.8% vs. 0.8%) than in the healthy control group ($p = 0.048$). In addition to ischemic heart disease, an increased risk of ischemic stroke was also found in a group with low IGF-1 levels 2.1 times higher than controls (Johnsen, 2005). The above data states the protective role of IGF-1 against cardiovascular diseases such as ischemic heart disease (IHD) and stroke.

The decrease in systemic NO synthesis is found to occur in patients with GH deficiency. This is due to the direct effect of IGF-1 that stimulates NO synthesis in endothelial cells. In a number of in-vitro studies, it was found that endothelial cells have IGF-1 receptors capable of directly mediating NO synthesis, thus modulating blood vessel tone (Castellano et al., 2009). The decrease in IGF-1 caused by GH deficiency is associated with increased platelet aggregation and decreased arterial dilatation, which in turn will affect endothelial function disorders and vasodilation processes. One study reported an increase in asymmetric dimethylarginine (ADMA), an endogenous NO synthesis inhibitor, which returned to normal levels after GH therapy (Setola, 2008).

Patients with GH deficiency also suffer from abnormalities in coagulation factors, such as elevated levels of Plasminogen activator inhibitor-1 (PAI), fibrinogen, and factor VIII (Di Somma et al., 2017). The risk of thrombosis is very high, therefore increasing the risk of cardiovascular morbidity and mortality (Beauregard et al., 2008).

4.2 Metabolic Effect

Abdominal obesity is one of the cardiovascular risk factors, due to its association with the incidence of atherosclerosis and arterial wall stiffness. Several studies have reported an increase in body fat mass, especially in abdominal adipose tissue, in patients with GH deficiency. Research showed a significant difference in the incidence of obesity ($p = 0.004$) between the GH deficiency group and the control group (27.77% vs. 8.4%) (Mo et al., 2014).

GH deficiency is often associated with impaired glucose metabolism that is characterized by insulin resistance and fasting hyperinsulinemia. The KIMS study, involving 6,050 GH deficiency patients who did not receive GH therapy, showed an increase in the prevalence of type II DM, especially in the women group (9.3% vs. 8.2%; CI 95% 1.04-1.23). This is due to increased BMI and impaired composition of body substances. Meanwhile, in patients with GH deficiency who did not have diabetes, about 9.5% exhibited an A1c value of 6-6.5% (Abs and Mattsson, 2013). Increased prevalence of Type II DM in GH deficiency was caused by increased insulin resistance, especially at hepatic level, and the inability of beta cells to compensate for resistance to insulin (Ciresi et al., 2015).

In addition, GH deficiency also causes lipid metabolism disorders. LDL-C and HDL-C are important markers of cardiovascular risk. High HDL-C levels are associated with a reduced risk of coronary heart disease, whereas high serum LDL-C increases the risk of heart disease (Newman, 2011). In patients with GH deficiency, there is often an increase in total and LDL cholesterol levels, whereas for TG and HDL levels, the effect is still controversial (Colao and Di Somma, 2002).

A study involving 863 control subjects and GH deficiency showed an increased incidence of hyperlipidemia (1.4% vs. 16.5%) in the GH deficiency group (Irie and Itoh, 2004). The hyperlipidemic incidence difference was significant between the two groups ($p < 0.0001$).

The interruption of lipid metabolism is due to the excessive production of VLDL apo B, where they

are the precursors of IDL and LDL apo B. In addition, in patients with GH deficiency there is also a decrease in VLDL clearance. Both of these may be associated with abdominal obesity that often occurs in patients with GH deficiency, where abdominal obesity coincides with insulin resistance increases VLDL-Apo B secretion from the liver (Castellano et al., 2009).

4.3 Effect of Growth Hormone Deficiency on Morphology and Heart Function

Structural disorders and heart function are reported to occur in patients with GH deficiency. Examination with echocardiography showed a decrease in the posterior wall thickness of the left ventricle (6.1 ± 1.1 vs. 9.04 mm; $p < 0.01$) and interventricular septum (7.1 ± 1.1 vs. 9.04 mm, $p < 0.01$), resulting in a decrease in left ventricular mass (54 ± 11 vs. 85 ± 15 g/m²; $p < 0.001$) and left ventricular internal diameter.

Researchers analyzed the performance of the left ventricle when the subject reached the peak of exercise using radionuclide angiography. There was significant impairment in left ventricular performance in the GH deficiency group, regardless of their age and age at the onset of the disease (Colao, 2008.). Therefore, it can be concluded that patients with GH deficiency, in general, had decreased cardiac performance during exercise.

In addition, in other studies it was found that young adult patients with GH deficiency will experience a decrease in left ventricular mass, decreased ejection fraction, as well as abnormal diastolic filling patterns. Then, associated with this, some researchers found a significant reduction of left ventricular systolic function, as well as decreased posterior left ventricular wall mass and interventricular septum (Cenci et al., 2009).

A study analyzed heart function in the GH deficiency group and control group using radionuclide scans and found a decrease in left ventricular ejection fraction and impaired heart function index (Colao, 2008).

4.4 Mortality Associated with Cardiovascular Events in Growth Hormone Deficiency

Since the early 1990s, several retrospective studies have shown an association between hypopituitarism and increased cardiovascular risk, especially in women with increased mortality associated with

cardiovascular and cerebrovascular diseases (Lombardi et al., 2012). Hypopituitarism patients with conventional therapy who did not receive GH substitution therapy had a shorter life expectancy.

For example, in a Swedish cohort study involving 344 patients with hypopituitarism, there was a twofold increase in mortality (RR = 2.17; CI 95% 1.88-2.51) compared with the general population. The risk of death was higher in women (RR = 2.93) than in men (RR = 1.91). In another British study that included 1,014 hypopituitarism patients, the risk of death was 1.87 times (95% CI 1.62-2.16 (Erfurth and Hagmar, 2005; Erfurth and Hagmar, 2005).

Increased mortality is caused by cardiovascular events (SMR 1.82, CI 95% 1.30-2.54) and especially by cerebrovascular events (SMR 2.44, 95% CI 1.54-4.18). In addition, in a study in Sweden the risk of death in the women group was found to be higher (RR = 2.29) than in the male group (RR = 1.57). High mortality in hypopituitarism patients who did not receive GH hormonal therapy was primarily due to cardiovascular events (1.82 CI 95% 1.3-2.54, $p < 0.0001$ (Tomlinson, 2001).

5 MARKER INFLAMMATION

C-Reactive protein (CRP) is a cardiovascular risk factor. In general, patients with GH deficiency have a 4-5-fold increase in CRP, suggesting a proinflammatory state (McCallum et al., 2005). In addition, other proinflammatory factors may also be involved in the pathophysiological mechanisms of cardiovascular complications associated with GHD. Among these, Interleukin (IL-6) and TNF- α have been shown to play an important role in causing endothelial dysfunction (Wong, 2013). In adult patients with GH deficiency, there is an increase in serum levels of IL-6 and TNF- α . So, the increase in proinflammatory cytokines is independent without being affected by obesity (Libby, 2012).

Increased concentrations of IL-6 are also independently related to the degree of CIMT. Recently, GHD has been shown to be associated with changes in adipokine protein expression patterns and an increase in adipose cell diameter. This leads to adipose tissue being susceptible to hypoxia and adipose dysfunction, thus also leading to chronic inflammation (Wong et al., 2012). Pregnancy-associated plasma protein-A (PAPP-A) has been shown to increase in GHD patients. This is interesting, because PAPP-A is a cardiovascular risk

factor and mediator of IGF-1 bioavailability (Joaquin and Aguilera, 2008).

5.1 Effect of rhGH Replacement Therapy on the Cardiovascular System

Despite the many controversies associated with cardiovascular disorders of patients with GH deficiency, current literature supports more superiority of rhGH therapy in improving cardiovascular risk factors in patients with GH deficiency.

One of the targets of rhGh therapy is heart mass. A rise in left ventricular mass is found in patients with GH deficiency in the early stages of GH therapy, whether children or adults. A meta-analysis of 16 trials involving 468 study subjects compared patients receiving GH therapy and those who did not.

There were significant positive effects of GH therapy on cardiac parameters assessed using echocardiography devices. Especially there was an increased left ventricular mass of 10.8 ($p = 0.02$). In addition, there was also an addition of 0.28 mm interventricular septal thickness ($p < 0.001$) and left ventricular posterior wall 0.98 mm ($p = 0.05$). On the other hand, at the cellular level, GH therapy may improve cardiac function through IGF-1 by increasing the sensitivity of myofilaments to calcium ions (Cenci et al., 2009).

Growth hormone therapy also has a positive effect on fat metabolism, especially total cholesterol, LDL, and HDL (van der Klaauw et al., 2006). GH therapy significantly reduces LDL cholesterol but does not affect TG. A meta-analysis of 37 RCTs also confirmed the neutral effect of GH therapy on TG levels, and concluded that there was a positive effect on total cholesterol and LDL levels (Cenci et al., 2009). In addition, a study showed an increase in ADMA which is a NO synthesis inhibitor, returning to normal value after the patient received GH therapy (Setola et al., 2008). In adult patients with GH deficiency who received GH hormonal therapy, there was a decrease in monocyte production and serum proinflammatory cytokine levels (Wong et al., 2012).

Table 1: Effects of growth hormone deficiency on the cardiovascular system.

 Effects of Growth Hormone Deficiency on the Cardiovascular System

1. Atherosclerosis
 - Improved CIMT
 - Increased IMA risk
 - Increased risk of ischemic stroke
 - Increased PAI, fibrinogen, factor VIII
 2. Marker Inflammation
 - Improved CRP
 - Increased TNF- α
 - Improved IL-6
 - Improved PAPP-A
 3. Metabolic Influence
 - Abdominal obesity
 - Dyslipidemia
 4. Morphology and Function of the heart
 - Decreased left ventricular posterior wall thickness
 - Decrease in the thickness of the interventricular septum
 - Decreased left ventricular mass index
 5. Mortality
 - Increased mortality associated with cardiovascular events
 - Increased mortality associated with cerebrovascular events
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